GW25-e2426

Characterization of bi-ventricular coronary flow reserve and remodeling in mice with pressure overload cardiac hypertrophy

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Objectives: Coronary microcirculation is critically involved in the cardiac adaption to pressure overload. Both clinical and high frequency ultrasound systems have been used to measure coronary flow in mice, but limited to the left coronary artery (LCA). The advent of high frequency Doppler flow imaging makes it possible to visualize the septal (SCA) and right (RCA) coronary arteries in a mouse model of pressure overload induced by transverse aortic constriction (TAC). Here, using high frequency Doppler ultrasound, we aimed to evaluate the flow patterns of the LCA, SCA and RCA in mice with TAC, and associate the flow parameters with corresponding structural and functional changes of both ventricles.
Methods: Forty-eight male C57BL/6J mice were subjected to TAC or corresponding sham operation. At 2 and 8 weeks post surgery, Doppler flow spectra from the three coronary arteries, together with echocardiographic structural and functional parameters of the left and right ventricles, were measured. Histology was performed to evaluate cardiomyocyte size and neoangiogenesis in both ventricles.
Results: In sham-operated mice, the LCA and SCA both showed low flow waveforms during systole and dominantly higher flow waveforms during diastole. The RCA exhibited generally lower flow velocity, with similar systolic and diastolic waveforms. TAC significantly increased the systolic flow velocities of all coronary arteries, but enhanced the flow mainly in the LCA and SCA. In the left ventricle, compared with sham-operated animals, coronary flow reserve (CFR) was partially preserved at 2 weeks post TAC (2.37±0.20 vs. 1.70±0.22 for LCA, $P<0.05$; 2.12±0.16 vs. 2.19±0.23 for SCA, $P>0.05$), but decreased at 8 weeks (2.48±0.23 vs. 1.75±0.17 for LCA, $P<0.05$; 2.34±0.22 vs. 1.58±0.12 for SCA, $P<0.05$), consistent with increased angiogenesis and negligibly changed systolic function at 2 weeks after TAC, but prominently blunted angiogenesis and systolic function at 8 weeks after TAC. In contrast, no significant change was found in the CFR, structure or function of the right ventricle.
Conclusions: This study has established an echocardiographic protocol for assessment of the flow pattern in three principal coronary arteries in mice and demonstrated the difference among three vessels and bi-ventricular remodeling at baseline and in pressure overload. Under TAC, it's elevated ventricular pressure rather than coronary perfusion pressure, causes structural and functional change as demonstrated in the RCA and right ventricle. The difference in the associating pattern of the coronary flow dynamics with the myocardial structure and function between the left and right ventricles facing distinctive loading conditions provides further insights into pressure overload induced ventricular remodeling.

GW25-e2513

To study the diagnostic value of matrix metalloproteinase -9 in ST segment elevation myocardial infarction by ROC curve

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Objectives: Matrix metalloproteinase-9 (MMP-9) is regarded as a biomarker of plaque rupture or vulnerability and is elevate in patients with acute coronary syndrome (ACS). The aim of the present study was to evaluate the diagnostic value of MMP-9 in ST segment elevation myocardial infarction (STEMI) by using receiver operating characteristic (ROC) curve and compared with creatine kinase-MB (CK-MB).
Methods: From September 2011 to February 2012, according to the "Chinese guideline of diagnosis and treatment: of acute ST-segment elevation myocardial infarction (STEMI) " (2010) established by the expert group in Chinese Society of Cardiology of Chinese Medical Association and Editorial Board of Chinese Journal of Cardiology, we selected 55 cases of STEMI in Coronary Care Unit (CCU) at the Heart Center of The First Affiliated Hospital of Xinjiang Medical University as our STEMI experimental group. Meanwhile, 50 cases in general ward at the Heart Center with symptoms of atypical chest pain but no abnormality of left and right coronary arteries in coronary angiography were selected as our control group. As the STEMI patients' myocardial infarction symptom occurred, we made the experiment based on the following different length of time after the symptom onset respectively: t≤4h (called Group ≤4 h), 4<t≤8h (called Group 4h<t≤8h), 8h<t≤12h (called Group 8h<t≤12h), 12h<t≤24h (called Group 12h<t≤24h), 24h<t≤48h (called Group 24h<t≤48h). The experiment included the measuring to the expression levels of MMP-9 in the plasma and the creatine kinase-MB (CK-MB); as well as using ROC curve to evaluate the diagnostic value of MMP-9 and CK-MB for STEMI.
Results: In STEMI patients, the levels of MMP-9 were 1.53±0.90 μg/ml (t≤4h, $P<0.001$), 1.49±0.88μg/ml (4<t≤8h, $P<0.001$), 1.65±0.79 μg/ml (8h<t≤12h, $P<0.001$), 1.89±0.72μg/ml (12h<t≤24h, $P<0.001$), 1.81±0.71μg/ml (24h<t≤48h, $P<0.001$) all significantly higher than the control group (0.20±0.02μg/ml). In addition to the ≤4 h group (48.69±58.37U/L, $P=0.131$), the levels of CK-MB in STEMI patients were 114.06±81.55 U/L (4<t≤8h, $P<0.001$), 143.96±127.05 U/L (8h<t≤12h, $P<0.001$), 123.79±126.82 U/L (12h<t≤24h, $P<0.001$), 74.33±140.62 U/L (24h<t≤48h, $P=0.003$) significantly higher than the control group (11.62±4.09 U/L). On ROC curve analysis, areas under the curve (AUC) of STEMI were 0.987, 0.949, 0.995, 0.989 and 0.977 for MMP-9; Youden index were 0.880, 0.869, 0.962, 0.944 and 0.944, respectively. The AUC of CK-MB were 0.852, 0.967, 0.976, 0.955 and 0.870, and Youden index were 0.642, 0.855, 0.927, 0.873 and 0.687 in STEMI, respectively.
Conclusions: MMP-9 level was elevated earlier than CK-MB and had a higher diagnostic value for early STEMI and for late STEMI.

GW25-e2515

Macrophage migration inhibitory factor in predicting short- and long-term major adverse cardiovascular events in patients with ST-segment elevation myocardial infarction

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Objectives: Macrophage migration inhibitory factor (MIF) play an important role in plaque development and stability, serve as a marker of early acute coronary syndrome (ACS) and of plaque instability. In the present study we aimed to assess the capacity of MIF to predict short- and long-term major adverse cardiovascular events (MACE) in ST-segment elevation myocardial infarction (STEMI) patients.
Methods: Prospectively consecutive included 90 patients admitted to coronary care unit (CCU), The First Teaching & Affiliated Hospital, Xinjiang Medical University, with a first STEMI from September 2011 to May 2013. Meanwhile, we recruited 44 patients with chronic stable angina (CSA) from the general ward of Heart center, and 44 healthy consecutive volunteers from the Medical Examination Center. MIF plasma concentrations were measured in 90 STEMI patients, 44 CSA patients and 44 healthy consecutive volunteers on admission. The endpoints of the study was MACE, The median follow-up was 18 months.
Results: The level of admission MIF was significantly higher in STEMI patients (91.99 (70.64-121.05) ng/mL) than CSA patients (52.25 (41.04-70.71) ng/mL, $P<0.001$) and healthy controls (18.44 (13.39-30.17) ng/mL, $P<0.001$). During hospitalization, 10 MACE occurred, the independent predictors of in-hospital MACE were: admission MIF (OR 1.00 95% CI 1.00-1.00, $P=0.038$, per each ng increase), admission greatinine (OR 1.04 95% CI 1.01-1.08, $P=0.006$, per each umol increase) and AUC CK-MB (OR 1.00 95% CI 1.00-1.00, $P=0.006$, per each U increase). The area under the receiver operating characteristic (ROC) curve with MIF used to predict in-hospital MACE was 0.77 (95% CI 0.64-0.89). A cut-off point of 104.38ng/mL showed a sensitivity of 70% and specificity of 66% for prediction of in-hospital MACE. During a median follow-up of 18 months, 9 MACE occurred, the independent predictors of long-term MACE were: admission MIF (HR 1.04 95% CI 1.01-1.07, $P=0.019$, per each ng increase), admission greatinine (HR 1.34 95% CI 1.12-1.60, $P=0.002$, per each mmol increase). The area under the ROC curve with MIF used to predict long-term MACE was 0.78 (95% CI 0.66-0.89), the cut-off value for the prediction of long-term MACE was 104.38ng/mL. In patients with MIF≥104.38ng/mL, the crude MACE rate was significantly higher compared to patients with MIF<104.38ng/mL (21% (6/29) vs. 6% (3/53), $P=0.04$) .
Conclusions: Our experimental and clinical findings indicate that a single MIF assay at admission could be a useful biomarker for early prediction of in-hospital and long-term MACE of patients with STEMI.

GW25-e3399

Catheter-based renal denervation lowers blood pressure in hypertensive mini-pigs

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Objectives: Although catheter-based renal denervation (RDN) shows a potent benefit in the treatment of resistant hypertension, there is a considerable controversy still exists on some aspects. The differentiation of individual-specific or model-specific response to RDN may be attributed to the different mechanisms involved in the maintenance of hypertension. This study was performed to investigate the effect of RDN on blood pressure (BP) and renal function in spontaneous hypertensive mini-pigs.
Methods: 16 spontaneous mini-pigs were divided into three groups: sham group (n=6), Sniper RDN group (n=5), and Symplicity RDN group (n=5). After measurement of the baseline BP and renal function, the bilateral RDN was performed using the Sniper (APT Medical Inc., Shenzhen, China) and Symplicity (Medtronic Inc., Minneapolis, MN) system, respectively. 12 weeks after the procedure, BP and renal function were measured, renal arteries were histological analyzed, and the renal arterial angiography was performed.
Results: The three groups of mini-pigs had similar systolic (sham 187.8±9.6, Sniper 186.0±13.3 Symplicity 169.4±7.7 mmHg, $P>0.05$) and diastolic (sham 136.8±6.5, Sniper 134.0±9.7 Symplicity 126.0±6.2 mmHg, $P>0.05$) BP at baseline. 12 weeks after the RDN procedure, the systolic (sham 192.4±10.5, Sniper 113.8±14.4, Symplicity 115.6±11.1 mmHg, sham vs. Sniper $P<0.01$, sham vs. Symplicity $P<0.01$) and diastolic (sham 141.2±5.9, Sniper 79.4±11.7, Symplicity 79.8±12.1 mmHg, sham vs. Sniper $P<0.01$, sham vs. Symplicity $P<0.01$) BP were significantly lowered

in Sniper and Simplicity group compared with sham group. However, there is no difference in the BP between Sniper and Symplicity groups. There were no significant changes in serum levels of creatinine and urea. Renal nerves were significantly destroyed in Sniper and Simplicity group. Additionally, there was no significant stenosis of renal artery at 12-week angiographic follow-up.
Conclusions: Catheter-based RDN with the Sniper or Symplicity system lowers BP in hypertensive mini-pigs without a significant renal dysfunction and stenosis of renal artery.

GW25-e4419

Polymer-free dual drug-eluting stents improve endothelialization of stenting coronary artery in a porcine model and the mechanism

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Objectives: To evaluate the endothelialization level of the polymer-free dual drug-eluting stents (DDES) compared to bare metal stents (BMS), polymer-free probucol stents (PES) and polymer-free sirolimus stents (SES) which has been used clinically in a overexpansion porcine coronary model, demonstrating the potential superiority in DDES group with the mechanism of homing more endothelial progenitor cells on local stenting coronary artery.
Methods: Total 160 stents of 4 types-BMS, polymer-free probucol stents (PES), SES and DDES-were randomly assigned and placed in 80 pigs (two stents per pig). At 14 days, 28 days, 90 days and 191 days after implantation, quantitative coronary analysis (QCA), intravascular unltrasound (IVUS), optical coherence tomography (OCT) were repeated on 20 pigs respectively, then stenting coronary arteries were collected after sacrifice the pigs for further study, one part of each artery for scanning electron microscope (SEM), histomorphology and histopathology, the other part for analysising the relative expression quantity of CD31, CD34 and CD133 on mRNA and protein level.
Results: There were not significant differences in lumen loss of QCA, neointima area of IVUS, OCT and HE stain, neointima volume of IVUS, injury scores, inflammation scores and endothelialization scrores of HE stain at the 4 endpoint among the 4 groups. Struts coverage percentage of OCT in PES group (59.37%±22.68%) was higer than SES group (20.11%±9.30%, P=0.001) and DDES group (36.62%± 20.54%, P=0.029) significantly, SEM result demonstrated the same trend. At 28 days after implantation, CD31 mRNA relative expression quantity in PES group (3.61±1.46) was higher than in BMS group (1.39±0.62, P=0.003), SES group (1.99±0.37, P=0.018) and DDES group (1.45±0.47, P=0.004). At 191 days after implantation, CD31 mRNA relative expression quantity in DDES group (11.01±5.90) was higher than in BMS group (2.02±1.10, P=0.009) and PES group (2.82±1.95, P=0.021). CD34 mRNA relative expression quantity in DDES group (4.21±1.27) was higher than in BMS group (0.85±0.36, P=0.009) and PES group (1.12±0.63, P=0.005). CD133 mRNA relative expression quantity in DDES group (3.39±1.35) was higher than in BMS group (0.75±0.51, P=0.003) and PES group (0.84±0.41, P=0.007). Unfortunately, the same variations were not exist on protein level.
Conclusions: Polymer-free dual drug-eluting stents can't further improve endothelialization of stenting coronary artery in the porcine model.

GW25-e4423

Beta-Blockers Should be Prohibited in Type-3 Long QT Syndrome with Marked Sinus Bradycardia

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Objectives: Encoding Nav1.5 sodium ion channels, mutations of SCN5A are responsible for type-3 long QT syndrome (LQT3) and sudden infant death syndrome (SIDS). This study aimed to determine the cause of sudden death (SD) in a Chinese teenager with markedly prolonged QT interval and a strong family history of SIDS.
Methods: Genotype-phenotype investigation was conducted in a Chinese family, in which the proband, a 12-year-old Chinese girl, was clinically diagnosed with LQTS and treated with beta-blockers as the baseline therapy. ECG screening and the candidate gene search of LQT1-3 were performed in the proband and her blood relatives. The acquired pcDNA-SCN5AWT/Mut was transfected into HEK-293 cells.Patch-clamp recording was performed to study the electrophysiological changes of the mutant ion channel after site-directed mutagenesis and transfection.
Results: The ECG of the proband showed a very slow heart rate for age (48 bpm, female at age 12), markedly prolonged QTc (660 ms) with late onset biphasic T waves that is typical to LQT3. On the 3rd day of metoprolol intake (50 mg/d), the proband died suddenly at rest. There were four SIDS cases in her family including her twin sister, her mother's sister and her manternal grandmother's sister. SCN5AMut (P.V411M), a point mutation, was identified in the proband and her mother (QTc 424ms). The functional effect of P.V411M was examined by patch-clamp analyses on HEK-293 cells. The peak current-voltage (I-V) relationship curves demonstrated that P.V411M produced a gain of function in the Nav1.5 channel The peak current density ws increased by 1.28 times compared to WT. The enhanced activation with a negative shift in the peak I-V relationship was significantly higher by -50mV voltage than WT (85.00%±7.43% VS 41.50 %±2.60%, P<0.01), while its voltage-dependent Na channel availability (SSI) curves were nearly unchanged, ranging from -140mV to 70mV voltage range.
Conclusions: SCN5A-P.V411M produced a gain of function in the Nav1.5 channel. P.V411M causes LQT3 and is high likely responsible for SIDS in this Chinese family. Beta-blockers are unsuitable to LQT3 with marked bradycardia, and perhaps should be prohibited.

GW25-e4430

Ibuprofen Attenuates Cardiac Fibrosis via Restoring the Imbalance of ACE and ACE2 in Diabetic Rat

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Objectives: Cardiac fibrosis is an important pathological change in the diabetic heart, and its induction and progression involves chronic inflammation. However, whether ibuprofen, a typical non-steroidal anti-inflammatory drug, has anti-fibrotic effect in the diabetic heart remains incompletely clear. This current study was to investigate the effects of ibuprofen on cardiac fibrosis in a rat model of type 1 diabetes.
Methods: Rats were grouped into: normal, diabetic, diabetic+ibuprofen and Rats were grouped into: normal, diabetic, diabetic+ibuprofen and diabetic+pioglitazone. The diabetic model was established by injecting streptozotocin (60 mg/kg, ip) into the rats. Then, ibuprofen (40 mg/kg/day) or pioglitazone (25 mg/kg/day) was given though a gavage for eight weeks. The amounts of collagen, laminin, α-smooth muscle actin (α-SMA) and fibroblast-specific protein 1 (FSP-1) were measured by histopathological and immunohistochemical analyses for assessing cardiac fibrosis. The major components of renin-angiotensin system, angiotensin converting enzyme (ACE), angiotensin II (AngII), angiotensin II type 1 receptor (AT1-R), ACE2, Ang (1-7) and Mas receptor (Mas-R) were detected by immunohistochemical and western blot analysis or ELISA assay. Transforming growth factor β_1 (TGF-β_1) and the mammalian target of rapamycin (mTOR) were evaluated by immunohistochemical and western blot analyses diabetic+pioglitazone. The diabetic model was established by injecting streptozotocin (60 mg/kg, ip) into the rats. Then, ibuprofen (40 mg/kg/day) or pioglitazone (25 mg/kg/day) was given though a gavage for eight weeks. The amounts of collagen, laminin, α-smooth muscle actin (α-SMA) and fibroblast-specific protein 1 (FSP-1) were measured by histopathological and immunohistochemical analyses for assessing cardiac fibrosis. The major components of renin-angiotensin system, angiotensin converting enzyme (ACE), angiotensin II (AngII), angiotensin II type 1 receptor (AT1-R), ACE2, Ang (1-7) and Mas receptor (Mas-R) were detected by immunohistochemical and western blot analysis or ELISA assay. Transforming growth factor β_1 (TGF-β_1) and the mammalian target of rapamycin (mTOR) were evaluated by immunohistochemical and western blot analyses.
Results: The serum glucose levels were increased and the body weight was decreased in the diabetic group compared with those in the normal group. Chronic treatment with ibuprofen decreased the levels of serum glucose, but had no effect on body weight. Excessive deposition of collagen, and increases in laminin, α-SMA and FSP-1 in the cardiac tissue were detected in the diabetic group. However, they were alleviated by ibuprofen treatment. The protein expression of ACE and AT1-R and the amount of AngIIwere higher, and the protein expression of ACE2 and Mas-R and the amount of Ang (1-7) were lower in the diabetic group. The ratio of ACE to ACE2 was raised in the diabetic group. All these changes were ameliorated by ibuprofen administration. In addition, the protein expression of TGF-β_1 and mTOR were raised in the hearts of the diabetic group and were attenuated by ibuprofen treatment. There was no significant difference between the ibuprofen and the pioglitazone groups.
Conclusions: The results suggested that treatment with ibuprofen could ameliorate the cardiac fibrosis in diabetic rats. The anti-fibrotic effects of ibuprofen were realized by reduction of ACE/AngII/AT1-R axis and enhancement of ACE2/Ang (1-7) /Mas-R axis, leading to the decrease of TGF-β_1 and mTOR expression.

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Endothelial-mesenchymal transition contributes to cardiac fibrosis induced by dyssynchronous heart failure through heterogeneity of mechanical stretch in a canine model

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Objectives: To explore the role and potential mechanism of endothelial-mesenchymal transition (EndMT) in dyssynchronous heart failure-induced cardiac fibrosis.
Methods: Twelve dogs received 3-week rapid right ventricular pacing to develop dyssynchronous heart failure and then were randomly divided into right ventricular pacing (RVP) group (n=6; kept RVP for another 3-week) and biventricular pacing (BiVP) group (n=6; changed to BiVP for 3-week), and another 6 dogs were selected as control group (sham operation). EndMT were respectively assayed by confocal microscope (Z-stack) in heart samples and western blot in cardiac endothelial cells from fresh heart fragments.
Results: BiVP slightly improved contractile function compared with RVP (P<0.05), but two groups still remained significant heart failure and similar ventricular dilatation. RVP induced significant cardiac fibrosis, elevated collagen 1A2 expression and depressed bone morphogenetic protein 7 expression in left ventricular lateral wall (late-contracting and high-stress) compared with anterior wall, which could be alleviated by BiVP. EndMT, transforming growth factor-beta (TGF-β) /snail signaling, collagen 1A2 and integrin β_1 expresson were significantly elevated in the endothelial cells from RVP lateral wall but reversed by BiVP. In vitro study, cyclic stretch could independently induce EndMT and enhance the pro-EndMT effect of TGF-β in HUVECs, which could be partly blocked by integrin β_1 siRNA.